Effect of a coordinating pyridine moiety on the SAP and TSAP isomer populations of bimodal Lanthanide (III) complexes

Marisa Poveda and Osasere Evbuomwan Ph.D.
Department of Chemistry, University of San Francisco, 2130 Fulton St., San Francisco, CA 94117

Introduction

PARACEST

Paramagnetic Chemical Exchange Saturation Transfer (PARACEST) agents are lanthanide complexes that generate MRI contrast through the slow-to-intermediate exchange of paramagnetically-shifted protons or water molecules.

CEST involves two exchangeable pools of protons, A and B. Protons in Pool B are saturated with a selective radiofrequency (RF) pulse. The protons between Pool A and B exchange with one another, decreasing the signal intensity of Pool A. This creates a darkening contrast.

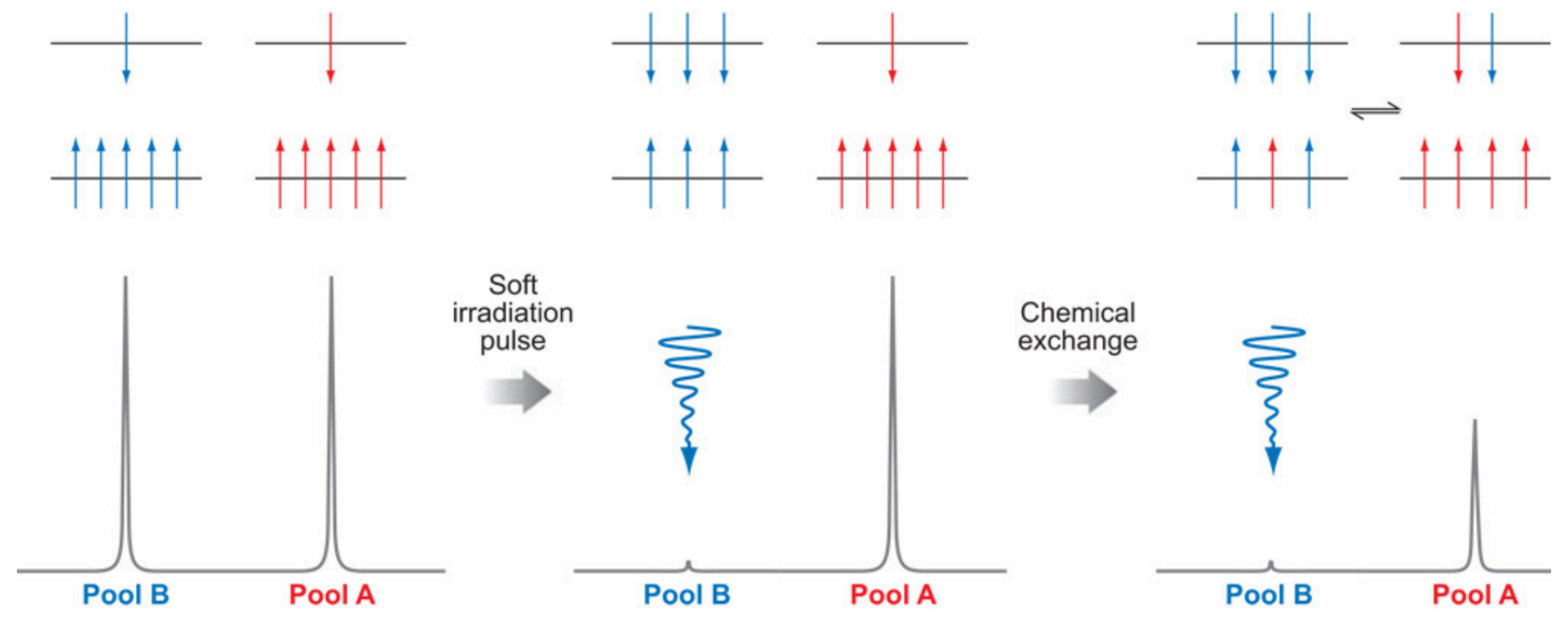

Figure 1: Chemical exchange saturation transfer of protons between pool A and B

In-vivo imaging studies of PARACEST agents have been limited due to the masking of the CEST signal by spin-relaxation exchange (T_{2ex}) and Magnetization Transfer (MT) effects. T_{2ex} causes a darkening of the image before the RF pulse can be applied by decreasing the bulk water signal similarly to the CEST mechanism. The MT window is a broad signal from endogenous macromolecules in tissue spanning ±100ppm that obscures the proton exchange signal.

Isomer Geometries

Ln(III)DOTA-tetraamides adopt either square antiprismatic (SAP) or twisted square antiprismatic (TSAP) geometries in solution that are in dynamic equilibrium with one another.

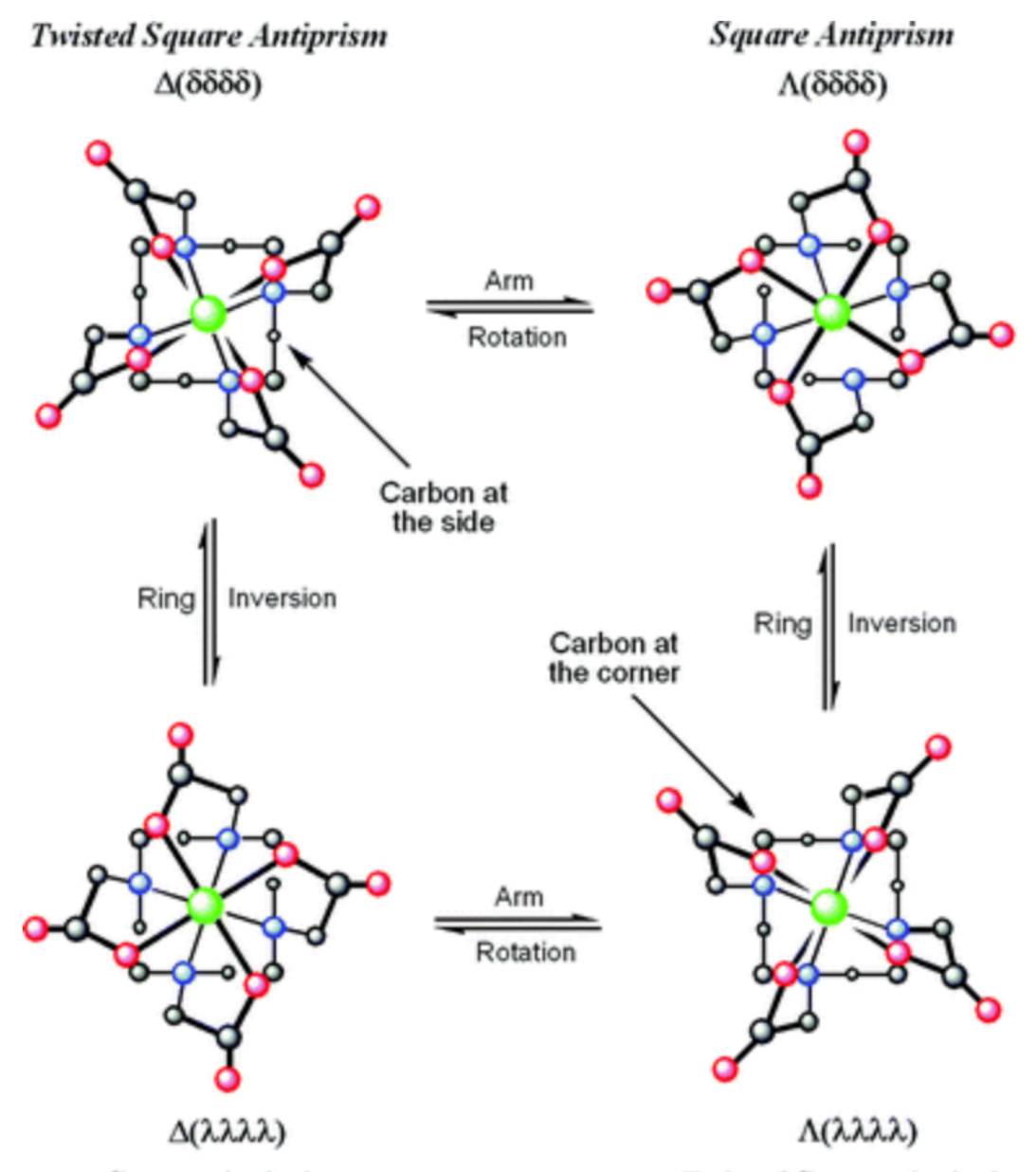

Figure 2: SAP and TSAP isomer geometries

Characteristics of the SAP isomer

- Compact
- Slower bound-water exchange kinetics
- Preferred for PARACEST applications that rely on water exchange as primary contrast mechanism

Characteristics of the TSAP isomer

- Faster bound-water exchange kinetics
- Preferred for PARACEST applications that rely on amide proton exchange as primary contrast mechanism

Project Goal

The goal of this project is to overcome both the T_{2ex} and the MT effect by developing complexes that preferentially adopt the TSAP geometry and induce contrast through amide proton exchange. We hypothesize that the presence of a coordinated pyridine moiety will cause primary adoption of the TSAP geometry.

Methods

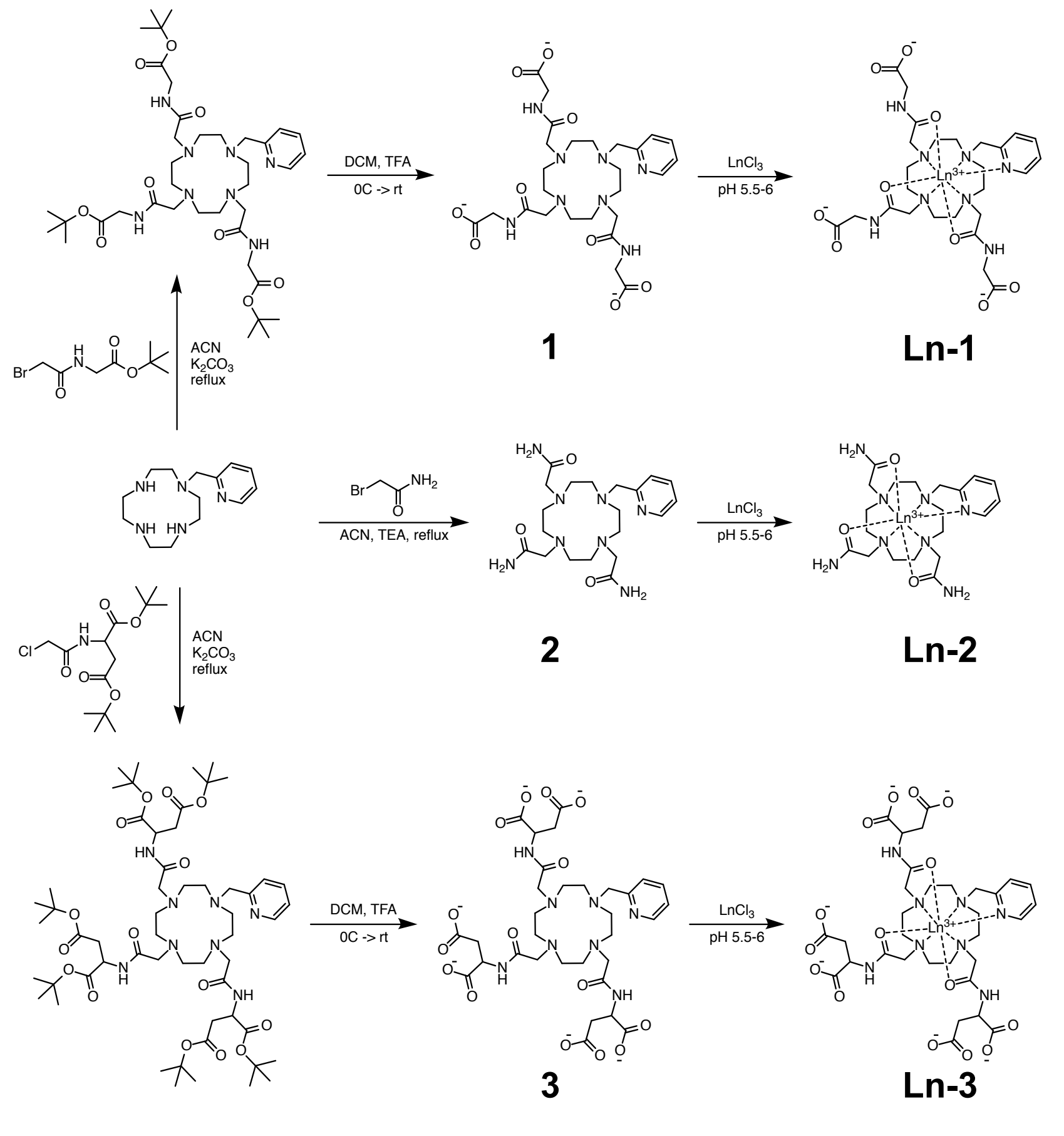

Figure 3: Synthetic scheme of **Ln-1**, **Ln-2**, and **Ln-3**. Lanthanides studied in this analysis are Tb^{3+} and Eu^{3+}.

Reagents and Materials

All reagents and solvents were purchased from commercial vendors.

Synthesis and Characterization

Lanthanide complexes in this study were synthesized according to Figure 3. All compounds were purified by Flash Chromatography or recrystallization and their identities verified by ^{1}H and ^{13}C NMR spectroscopy.

Results and Discussion

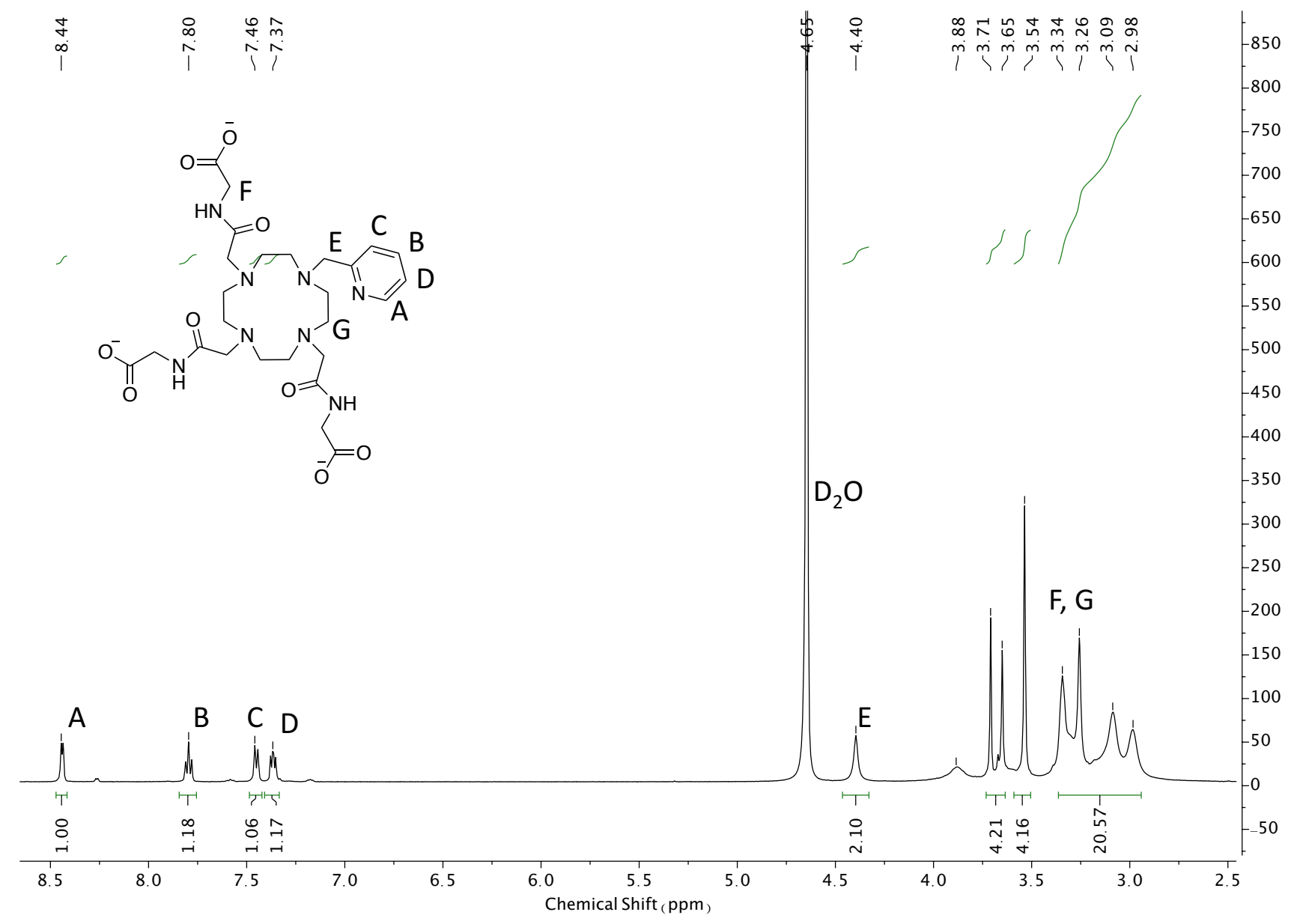

Figure 4: ^{1}H NMR of **1** was acquired in D_2O at field strength 500 MHz.

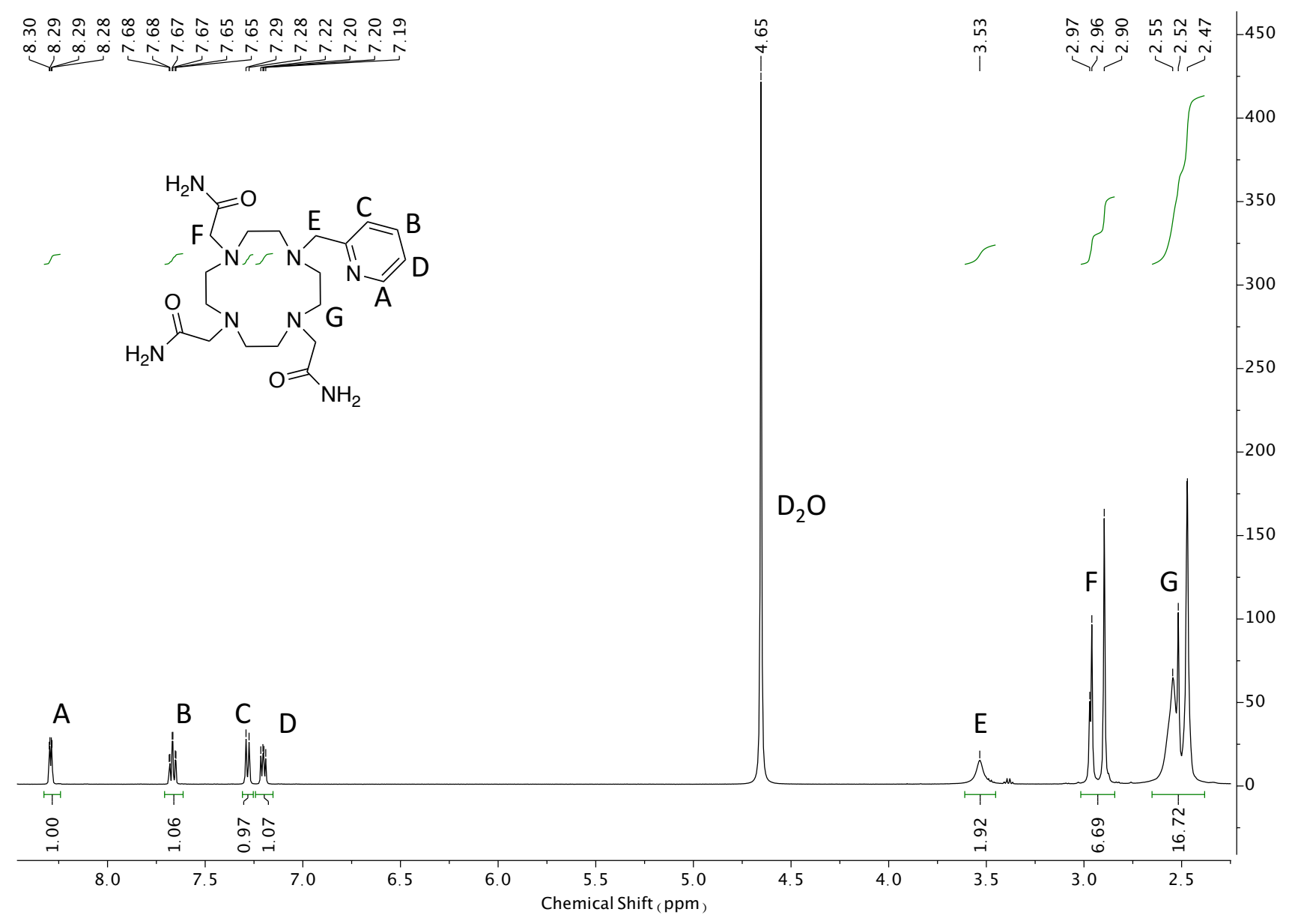

Figure 5: ^{1}H NMR of **2** was acquired in D_2O at field strength 500 MHz.

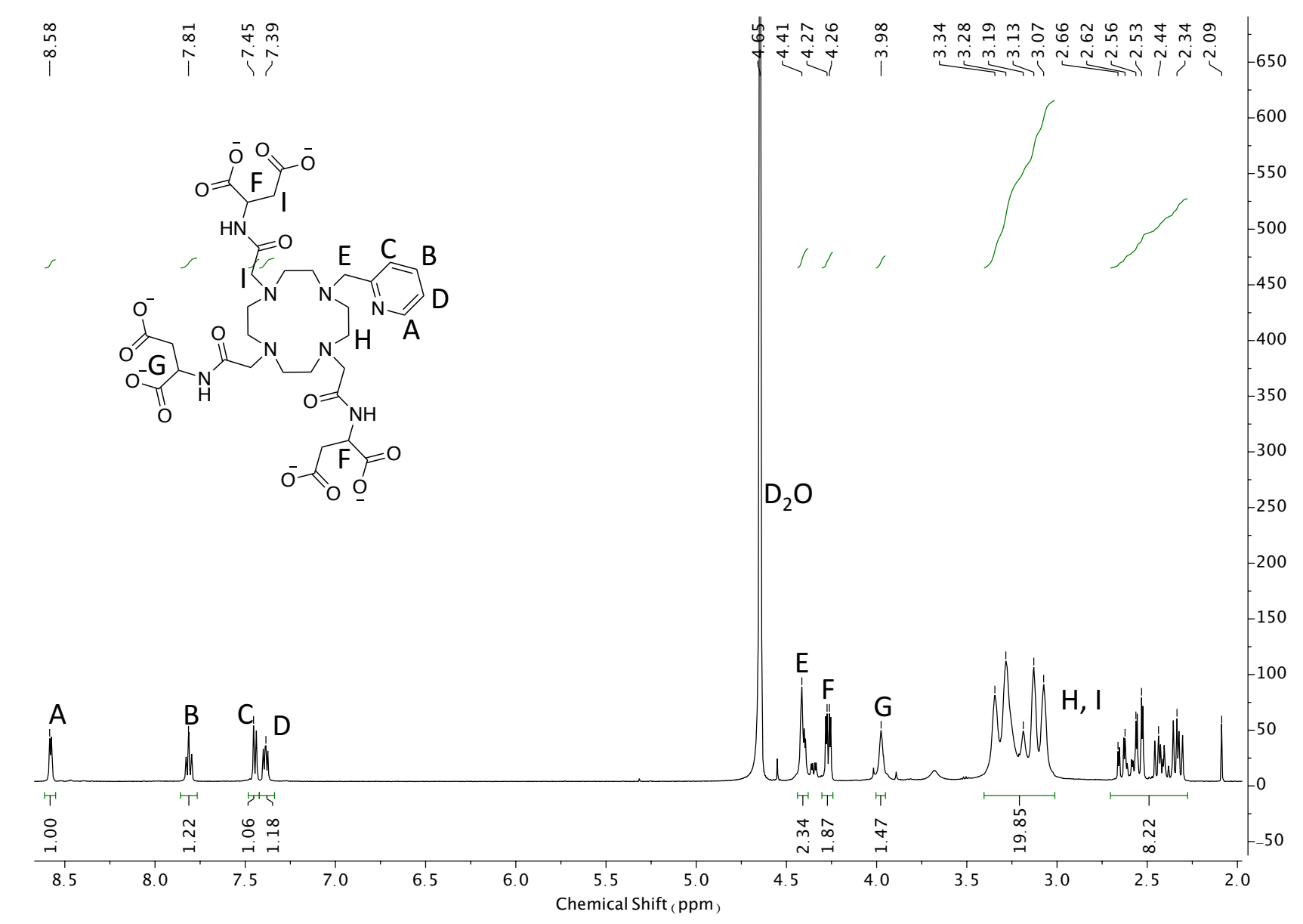

Figure 6: ^{1}H NMR of **3** was acquired in D_2O at field strength 500 MHz.

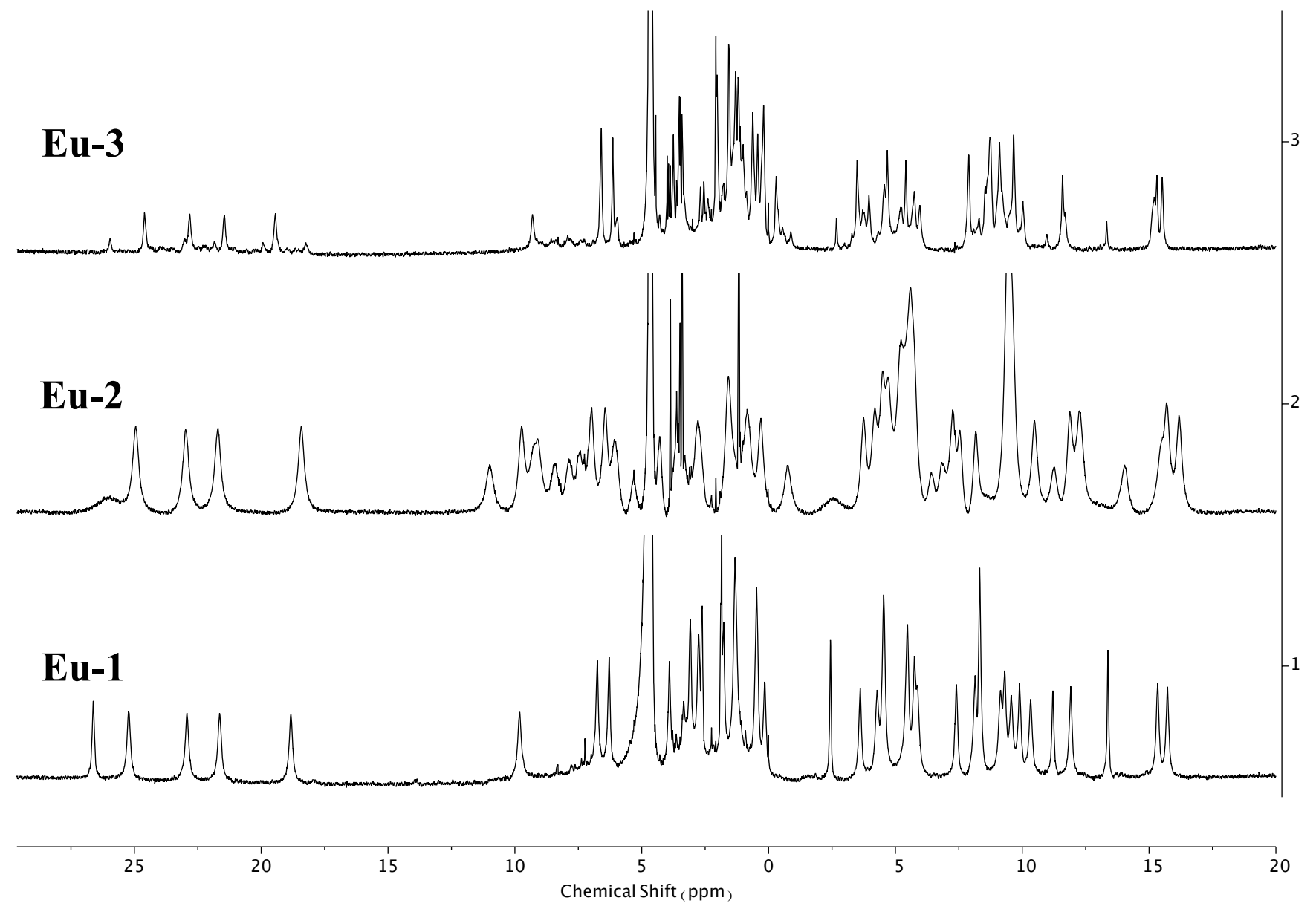

Figure 7: NMR of **Eu-1**, **Eu-2**, **Eu-3.** were acquired in D_2O at field strength 500 MHz.

^{1}H NMR Characterization

- ^{1}H NMR spectroscopy confirmed ligands **1-3** were synthesized successfully.
- ^{1}H NMR of the Ln complexes show an expanded chemical shift window due to the lanthanide induced shift from the metal ion.
- The difference in chemical shifts in the ^{1}H NMR is due to the different chemical environments induced by the ligands.

Luminescence

- **Eu-1, Eu-2,** and **Eu-3** emitted red light characteristic of Eu^{3+} ions.
- **Tb-1, Tb-2,** and **Tb-3** emitted green light characteristic of Tb^{3+} ions.
- This shows evidence of luminescence sensitization by the pyridine antenna.

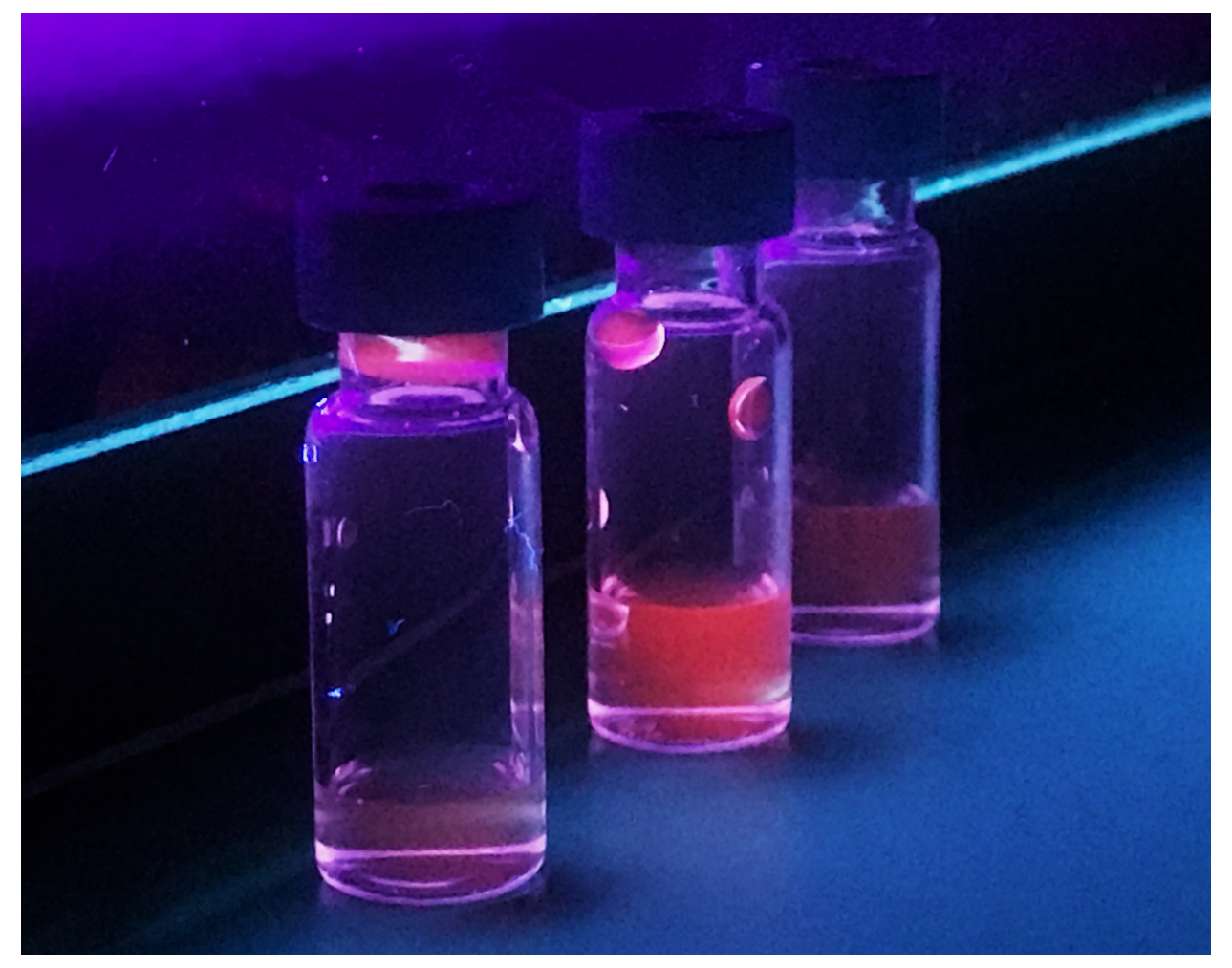

Figure 8: Images of **Eu-1**, **Eu-2**, and **Eu-3** solutions in D_2O upon excitation at 302 nm by a UV lamp

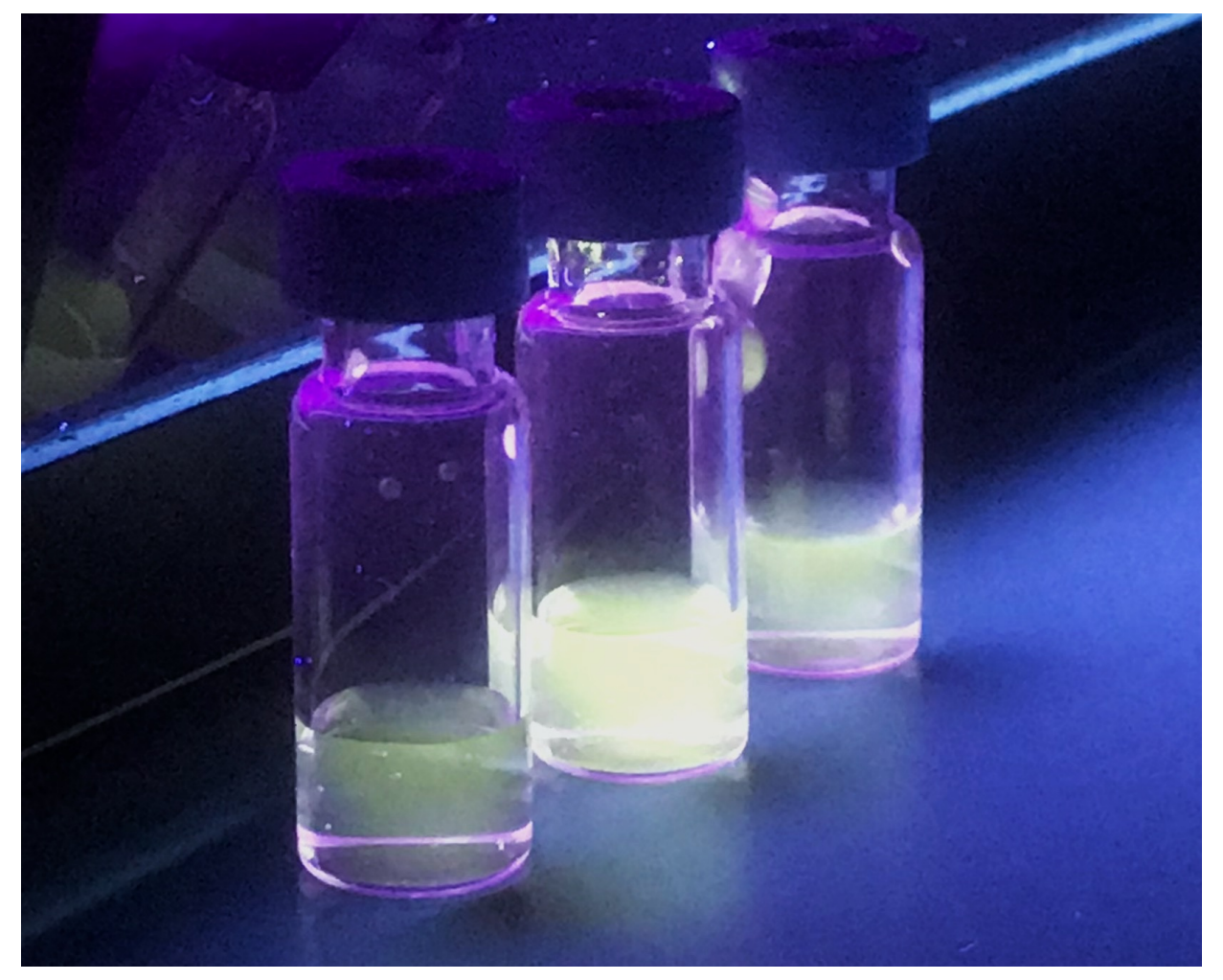

Figure 9: Images of **Tb-1**, **Tb-2**, and **Tb-3** solutions in D_2O upon excitation at 302 nm by a UV lamp

Future Work

- High resolution ^{1}H NMR analysis of Tb^{3+} and Tm^{3+} complexes
- Investigation of luminescence and PARACEST properties of the library of complexes
- Synthesis of a new library of complexes with an appended quinoline antenna

References

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2. Woods, M.; Botta, M.; Avedano, S.; Wang J.; Sherry, A. D. *Dalton Trans.*, **2005**, 3829
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